Household members should have tuberculin skin tests done as well because the initial contact is usually an adult in the household.

In view of the permanently destructive nature of the disease process, it is important to initiate therapy as soon as possible, with three first-line antituberculosis medications (such as INH, ethambutol, rifampin and streptomycin). Chemotherapy may be altered when sensitivities are determined; however, two-drug therapy is warranted for at least a year. Adherence to a therapeutic regimen of appropriately selected antibiotics effectively halts the disease process. Following successful pharmacotherapy, surgical intervention may be considered for many patients, particularly those who had a prolonged course of illness before effective treatment.[16] Necrotic tissue may be removed via a mastoidectomy.

Tuberculous otitis is a condition readily amenable to appropriate antituberculous chemotherapy. In any otitis which does not respond to the usual antibiotic therapy, or which presents as a painless otorrhea, tuberculosis must be suspect, and PPD testing should be routinely done in these patients. Most of the hearing defict present at the time of initial treatment will be permanent, but further loss can be prevented and progression to a life-threatening meningitis aborted.

Summary

Tuberculosis is a rare cause of middle ear suppuration in the United States today, although with an increase in foreign travel and migration there has been a recent rise in the number of cases, especially of extrapulmonary tuberculosis. In patients presenting with chronic, painless otorrhea or chronic otitis media that does not respond to the usual antibiotic therapy, tuberculous otitis should be considered. The diagnosis is important as tuberculous otomastoiditis is a rapidly progressive, irreversibly destructive process, and effective therapy should be instituted early. The two cases described above represent the characteristic features of this disease and illustrate the severe hearing deficiencies that can result in children. Tuberculous otitis media has been associated with serious consequences, including rapidly progressive permanent deafness and progression to fatal meningitis.

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Hypercalcemia, Pneumothorax and Pneumoperitoneum in a Patient With Pulmonary Mycobacteriosis and Esophageal Carcinoma

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ALTHOUGH CARCINOMA of the esophagus remains one of the least common of all malignant conditions to afflict people in the United States, its prevalence and age-adjusted death rate has been rising slowly but steadily over the past 50 years, particularly among nonwhite Americans. Based on death rates from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program (1973 through 1976), the esti-

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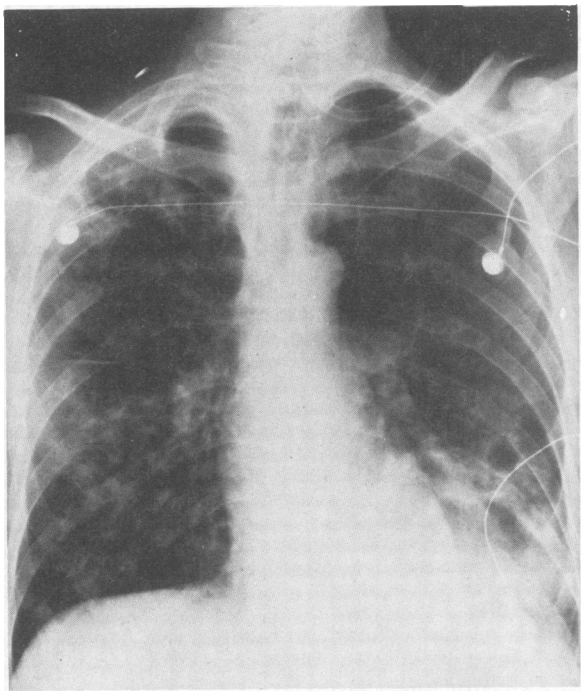

Figure 1.—Roentgenogram of the chest, with the patient upright, on May 28, showing bilaterial infiltrates with right upper and left lower lobe cavitation.

mated mortality from esophageal cancer in 1979 will be 8,400 in a total of 395,000 cancer deaths (2.1 percent).[1] The rising mortality has been attributed to increased longevity and better case-finding techniques.

About 80 percent of esophageal carcinomas present as obstructing lesions. Symptoms, however, frequently appear late.[2,3] When obstruction is absent, symptoms may arise as a result of extension of the carcinoma to contiguous structures or metastasis to distant sites, thus delaying diagnosis further.

This paper presents a case of esophageal carcinoma in which several uncommon features prevented physicians from making a precise diagnosis. The carcinoma occurred in a patient with underlying pulmonary mycobacteriosis. Of particular interest was the chest barotrauma which accompanied the terminal stages of the patient's illness.

Report of a Case

Ten days after receiving an aortobifemoral bypass graft for Leriche syndrome at another hospital, a 44-year-old Cuban man was readmitted to hospital in May 1978 with a four-day history of productive cough and fever.

As a youth, the patient had been told he had pulmonary tuberculosis. A few years before admission, a roentgenogram of the chest taken at a public health clinic showed "scarring at the right apex." He had a history of 60 pack-years of cigarette smoking as well as 15 years of heavy alcohol consumption and the presence of peptic ulcer disease, for which he took antacids. Recently, he had noted loss of appetite and substernal discomfort on eating. He had lost an unknown amount of weight during the six weeks before his operation.

A physical examination showed a thin man who appeared to be in no distress. Temperature was 37.6°C (99.6°F) and respirations 24 per minute. An examination of his lungs disclosed bilateral rhonchi. Hemoglobin was 9.9 grams per dl. The leukocyte count was 15,300 per cu mm with 79 percent polymorphonuclear cells, 3 percent band cells and 7 percent eosinophils. A roentgenogram of the chest showed a right apical infiltrate with cavitation and pleural thickening. Cytologic examination showed atypical cells not further classified. Sputum culture yielded *Proteus mirabilis* and *Candida* species. The patient was given chest physiotherapy, and penicillin, ampicillin and gentamicin were administered. He continued to lose weight and remained febrile, while chest roentgenograms showed development of bilateral alveolar infiltrates with cavitation in the left lower lobe. When sputum concentrates yielded acid-fast bacilli, he was transferred to Rancho Los Amigos Hospital on the 14th hospital day.

On admission to Rancho Los Amigos Hospital, a physicial examination showed the patient to be cachectic, but apparently in no acute distress. Temperature was 37.4°C (99.4°C), blood pressure 110/72 mm of mercury when supine, and 100/70 mm of mercury when sitting; pulse 104 beats per minute and respirations 18 per minute. Mucosae were pale, teeth were carious. The lungs were clear. There were no murmurs or gallops. Pulses in distal legs were diminished. There was a well-healed midline abdominal scar. Concentration was poor and there was slurring of words.

The hemoglobin value was 10.5 grams per dl and hematocrit 33 percent. The leukocyte count was 29,900 per cu mm, with 68 percent polymorphonuclear cells and 22 percent band cells. The platelet count was 347,000 per cu mm. Analysis of the urine showed trace protein, 5 to 10 leukocytes, 5 to 10 erythrocytes, and 10 to 20 hyaline and fine granular casts per high-power field.

Serum potassium was 4.9, sodium 135 and chloride 96 mEq per liter; blood urea nitrogen was 23, creatinine 0.8, glucose 118, calcium 13.4, phosphorus 3.1, magnesium 2.4 and uric acid 6.3 mg per dl; albumin was 2.5 and total protein 7.0 grams per dl; serum glutamic oxaloacetic transaminase (SGOT) was 28 (normal 7 to 40 mU per ml), lactic dehydrogenase (LDH) 177 (normal 100 to 224 mU per ml) and alkaline phosphatase 164 mU per ml (normal 30 to 85 mU per ml) and total bilirubin was 0.5 mg per dl. Serum protein electrophoresis showed depressed albumin, elevated α_1-globulin and broad band γ-globulin fractions.

Determinations of arterial blood gases while the patient breathed room air were as follows: oxygen pressure (Po_2) 53 and carbon dioxide pressure (Pco_2) 42 mm of mercury, pH 7.53 and bicarbonate 35 mEq per liter. A roentgenogram of the chest showed extensive patchy infiltrates bilaterally with cavitation in the right upper lobe. An electrocardiogram showed right atrial enlargement and changes consistent with chronic lung disease. Sputum culture grew *Proteus mirabilis,* but a urine culture yielded no growth. Sputum concentrates showed numerous acid-fast bacilli, and culture grew *Myobacterium avium-intracellulare* complex. Urine culture for acid-fast bacilli did not grow organisms. A lumbar puncture showed a normal opening pressure, no leukocytes, one erythrocyte per cu mm, and normal protein, glucose and glutamine concentrations.

The patient was treated with INH (isoniazid), ethambutol, and copious fluids given orally. His course was complicated by persistent hypoxemia, confusion, hypercalcemia and upper gastrointestinal bleeding. On the 17th hospital day, fever, hypotension and tachycardia suddenly developed. A repeat roentgenogram of the chest showed further extension of the left lower lobe infiltrate with cavitation (Figure 1). The patient was treated with nasogastric suction, antacids, penicillin, gentamicin, packed erythrocytes and intravenous fluids. Serum calcium rose to 14.6 mg per dl. Serum phosphorus was 2.4 mg per dl and chloride was 107 mEq per liter. Serum-intact parathyroid hormone (PTH) concentration by radioimmunoassay was 159 pg per ml. Normal range of PTH for serum calcium levels of 8.8 to 10.0 mg per dl is 255 ± 2 SD or 92 pg per ml, using an antiserum specific for intact PTH molecule, as measured by Laboratory Procedures, Esoteric Center, Kalamazoo, Michigan.

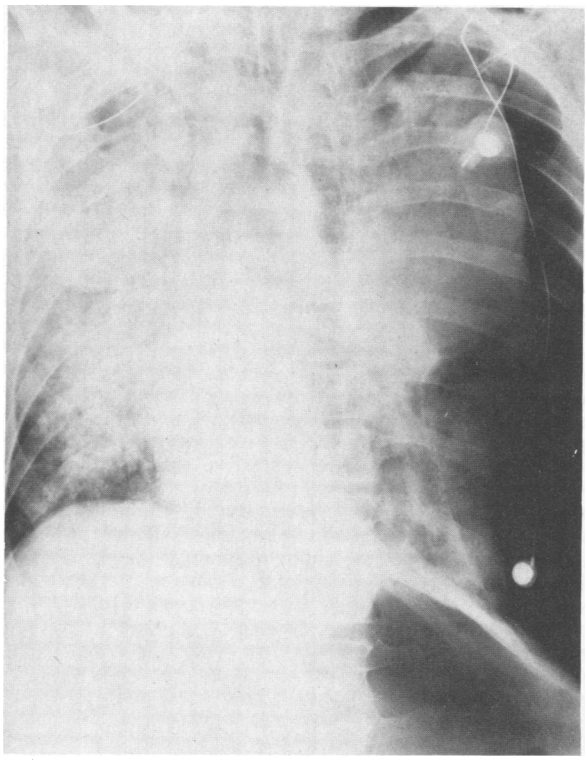

Figure 2.—Roentgenogram of the chest on June 2, showing large pneumothorax and pneumoperitoneum.

A liver scan on day 21 showed hepatomegaly with numerous filling defects. That evening the patient became acutely cyanotic and tachypneic. Secretions became copious. With the patient breathing room air, arterial blood gas determinations were Po_2 34 and Pco_2 60 mm of mercury and pH 7.22 A roentgenogram of the chest showed increasing consolidation throughout the left lung. Despite endotracheal intubation and assisted ventilation, respiratory function deteriorated.

On the 22nd day, the patient became hypotensive. The chest was hyperresonant on the left side with absent breath sounds. Another roentgenogram of the chest showed a large pneumothorax on the left, and free air under the diaphragm (Figure 2). During insertion of a tube into the chest ventricular tachycardia and fibrillation developed. The arrhythmia could not be corrected and the patient died despite resuscitation attempts.

Findings at Autopsy

At autopsy, a large, gritty, granular mass with central necrosis was found in the lower third of the esophagus. It infiltrated the wall and perforated into the trachea, mediastinum and left lower

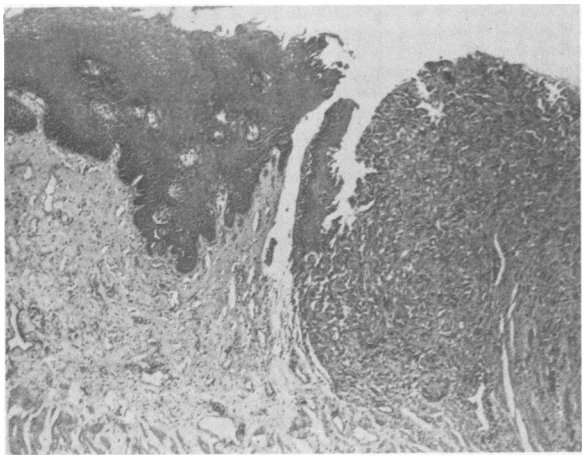

Figure 3.—Esophagus, with normal epithelium at left being abruptly replaced by infiltrating squamous cell carcinoma. This area was interpreted as the primary site. (Hematoxylin-eosin stain; reduced from magnification ×100.)

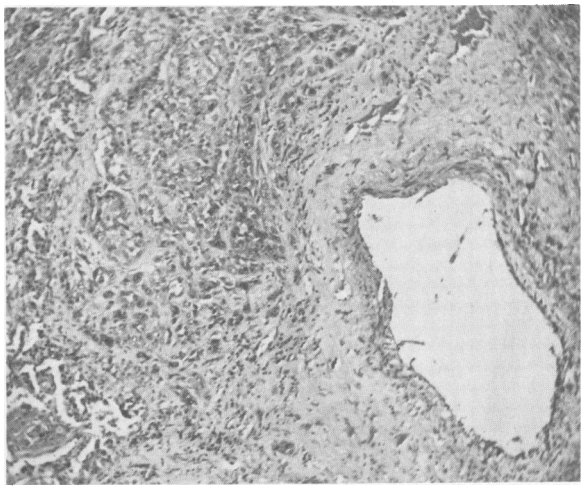

Figure 4.—Vessel in lung, with numerous nests of epidermoid carcinoma in periadventitial lymphatic channels. Tumor has infiltrated surrounding lung parenchyma and produced a metastatic mass. (Hematoxylin-eosin stain; reduced from magnification ×40.)

lobe. The tumor had formed a large mass with central cavitation which, in turn, communicated with the esophagus, trachea, lung and mediastinum. It had perforated the diaphragm. Histologic examination showed a mucoepidermoid carcinoma. In one area, it showed continuity with the squamous epithelial lining of the esophagus and invasion into the esophageal wall (Figure 3). There were metastatic lesions in both lungs, mediastinal nodes, liver, adrenal glands, kidneys, pancreas and myocardium.

Both lungs showed multiple cavities with caseation necrosis and typical tuberculous granulomata. Pneumonia, abscess formation, bronchiectasis and emphysema were widespread. Connection of the tumor masses with the trachea or bronchi was demonstrable, except in the area of the trachea contiguous with the lower esophagus. The neoplastic masses showed an epidermoid pattern. They were located at the periphery of the lung, often around a vessel which at times showed neoplastic cells in the lymphatics (Figure 4).

No evidence of metastasis was found in sections of vertebral bone (C-4 to coccyx). The distal aorta and iliac arteries were occluded by thrombi although the aortoiliac prothesis was patent. The parathyroid glands were not enlarged and were normal on microscopic examination. The brain and spinal cord were normal.

Discussion

Hypercalcemia

There are several unusual aspects of this case. First is the hypercalcemia which contributed to the patient's mental deterioration. Because the serum albumin was low, the proportion of unbound calcium ion was relatively increased, further augmenting his obtundent condition.

Hypercalcemia occurs in 16 percent to 56 percent of patients with carcinoma of the esophagus.[4] Some investigators feel that as many as two thirds of these cases are associated with ectopic parathyroid hormone production.[5] Others have been skeptical, citing the role of osteoclast-activating factor, prostaglandin E, sterols with vitamin D-like activity and immobilizaton.[4,6,7]

The cause of the hypercalcemia in this patient was probably ectopic PTH produced by the neoplasm, because he had no demonstrable bone metastasis and had an inappropriately high serum level of immunoreactive PTH for the degree of hypercalcemia manifested. The parathyroid glands were microscopically normal, ruling out primary hyperparathyroidism. Had the hypercalcemia been due to bone metastasis or other humoral factors, the concentration of PTH would have been undetectable.[8,9] In addition, near the end of his hospital course a high serum chloride to phosphorus ratio ($Cl/PO_4 = 107/2.4 = 40.4$) developed in the patient. Palmer and others have reported that the chloride to phosphorus ratio is higher than 33 in most patients with primary hyperparathyroidism as opposed to those with other causes of hypercalcemia.[10] Furthermore, they suggest that patients with ectopic PTH-producing tumors also

have high chloride to phosphorus ratios. A rise in the patient's phosphorus concentration would have suggested suppression of PTH by hypercalcemia induced by skeletal metastasis.[8] Increased urinary excretion of cyclic adenosine monophosphate (3′5′-cAMP) expressed as a function of glomerular filtration has also been found to be a very useful test indicative of excessive amounts of circulating active PTH.[11] Demonstration of PTH in the neoplastic tissue would have provided unequivocal proof of its source; however, these studies were not available.

The radioimmunoassay of PTH in our patient made use of the intact, biologically active form in the circulation. Benson and colleagues, and Hawker and Di Bella have found the radioimmunoassay to be useful in differentiating ectopic hyperparathyroidism due to neoplasia from primary hyperparathyroidism.[8,12] The COOH-terminal, biologically inactive fragment of the PTH peptide, which was not measured directly in our patient, is greatly decreased in ectopic hyperparathyroidism as compared with primary hyperparathyroidism. On the other hand, the quantity of circulating intact parathyroid hormone is similar in both groups.[8] Because intact PTH was measured in our patient and because this assay recognizes COOH-terminal fragments to a much lesser extent, it would explain why the assay would give a lower PTH level in a patient with suspected ectopic hyperparathyroidism than in a patient with primary hyperparathyroidism. Hawker and Di Bella have concluded that (1) the blood of patients with ectopic hyperparathyroidism contains predominantly intact immunoreactive PTH and (2) the blood of patients with primary hyperparathyroidism contains a form of immunoreactive PTH that is either not detected or is found only in small quantities in ectopic hyperparathyroidism, and that this is probably the COOH-terminal fragment.[13]

Riggs and others have suggested that nonendocrine tumors associated with hypercalcemia produce a larger (precursor) PTH molecule and this precursor may not be converted to a smaller form in these patients.[14]

Formation of Fistulas

The most common presenting symptom of esophageal carcinoma is dysphagia, a complaint that our patient had described vaguely.[2] However, about 20 percent of malignant lesions are nonobstructing when first detected.[3] When dysphagia is absent, unusual presenting symptoms may occur. For example, local extension can cause hoarseness due to involvement of the recurrent laryngeal nerve.[3] The incidence of esophagorespiratory communications is 5 percent to 10 percent.[15] Most such fistulas occur in the middle third of the esophagus, and are a result of spontaneous or radiation-induced necrosis of the tumor adjacent to the trachea or major bronchus. Our patient's condition was unusual in that the esophagobronchial fistula occurred in the lower third of the esophagus. Such patients, who are already suffering from advanced esophageal cancer and its treatment, begin to have sudden bouts of coughing, chest pain, hemoptysis, aspiration, pneumonia or sepsis.[3,15,16] The most common cause of death in patients with esophagorespiratory fistulas is not from the cancer itself, but from aspiration.[16] Treatment is difficult, and at best, palliative.[15,16]

When such a fistula is the result of a neoplasm, a question may arise as whether the tumor originated in the esophagus or the bronchus. Indeed, at our patient's autopsy, the presence of a large mass in both trachea and esophagus invading the mediastinum, pericardium and diaphragm initially gave the impression of a primary bronchogenic carcinoma, also suggested by the pattern of metastasis. However, careful dissection and histologic examination showed the site of origin in the esophagus, and failed to find any such foci in the tracheobronchial tree. The location and pattern of the nodules in the lungs also suggested their metastatic nature. In fact, it is rare for esophageal symptoms to develop as a result of invasion of the esophagus by bronchogenic carcinoma even late in the disease.

Barotrauma

The development of pneumothorax and pneumoperitoneum is very unusual in a patient with esophageal carcinoma and pulmonary mycobacteriosis. Chronic bronchitis and emphysema are the most common causes of spontaneous pneumothorax in patients over 40 years of age.[17] Less commonly, rupture of a caseating subpleural tuberculous lesion may lead to pneumothorax. Even more rare are pneumothoraces associated with intrathoracic neoplasms.[17] Metastatic sarcomas are the most common neoplasms associated with spontaneous pneumothoraces[18,19]; bronchogenic carcinoma is a rare cause.[20,21] A pneumoperitoneum associated with a *supradiaphragmatic*

neoplasm has not been previously reported. Likely mechanisms for these phenomena in our patient include:

- Rupture of a subpleural bleb in an area of emphysema or granulomatous cavitation, which may be facilitated by positive pressure ventilation.
- Invasion of the esophageal neoplasm into the lung parenchyma with subsequent rupture through the diaphragm into the peritoneal cavity.
- Direct invasion of the pleura by the esophageal neoplasm with necrosis, rupture or perforation.
- Air, forced into the lungs under high pressure, may rupture alveoli and dissect into the interstitial space or perivascular sheaths.[22,23] From here, it may dissect toward the hila, mediastinum and through the diaphragm into the retroperitoneal space. If air flow continues, the retroperitoneal space ruptures, releasing air into the abdominal cavity. On a roentgenogram of the chest (with the patient in an upright position), it can be noted that intraperitoneal air rises to the highest point below the dome of the diaphragm. It can be distinguished from retroperitoneal air which is at greatest volume medial or lateral to the highest point of the diaphragm.[24,25]

Pneumoperitoneum has been described most frequently in infants with respiratory distress syndrome who are treated with positive pressure ventilation.[26-29] Recently it has also been described in adults receiving assisted ventilation.[24,30] Usually a pneumothorax occurs before the pneumoperitoneum.[24,26] Pneumoperitoneum without evidence of pneumothorax favors a diagnosis of perforated intraabdominal viscus. However, when the two coexist, a perforation cannot be ruled out. A rupture of the gastrointestinal tract would be suggested by air-fluid levels seen intraperitoneally on a roentgenogram of the patient in an upright position,[31] and can be verified by administration of a water-soluble contrast material.

Had the patient's condition permitted, further diagnostic studies such as esophagography, esophagoscopy and bronchoscopy would have led to the precise diagnosis and, perhaps, an explanation for the radiographic findings. Unfortunately, inanition, hypercalcemia and rapid progression of respiratory failure prevented such investigations.

In conclusion, esophageal cancer can present with uncharacteristic clinical, laboratory and radiographic findings, and not all patients will have dysphagia and aspiration when first seen. Physicians who are aware of the pathophysiological events that occur with this disease will be better prepared to deal with them, if only to allow the patient's decline to be more tolerable.

Summary

Coughing and fever developed in a 44-year-old man shortly after an aortofemoral bypass operation. A roentgenogram of the chest showed bilateral infiltrates with cavitation. The patient's course of illness was complicated by hypercalcemia, progressive obtundation and respiratory failure, making assisted ventilation necessary. Shortly before death, pneumothorax and pneumoperitoneum developed. At autopsy, findings included active pulmonary disease due to *Mycobacterium avium-intracellulare* complex and esophageal carcinoma invading the lung, mediastinum and diaphragm.

Hypercalcemia, an unusual feature of esophageal cancer, was probably caused by ectopic production of parathyroid hormone, which was shown to be present in the serum by radioimmunoassay for the intact molecule. The most unusual aspect of this case was pneumothorax, occasionally reported with intrathoracic tuberculosis and neoplasms, and pneumoperitoneum. Mechanisms that can account for these phenomena were discussed.

While dysphagia is the most common presenting symptom of esophageal cancer, physicians should also be aware of these unusual manifestations.

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Evaluating Thyroid Nodules

THE CRITERIA that are most helpful in evaluating thyroid nodules are their size, shape and consistency. Nodules that are over 2 to 2½ cm, that by their consistency suggest anything of a hard or infiltrating quality, and that have a rate of growth that is persistent and progressive, are nodules that should be removed. The sex of the patient is germane in this situation . . . more nodules are found in females than males. When there is a nodule in a male . . . there is an increased index of suspicion and a lower threshold for wanting to proceed with an operation. History of ionizing radiation is important. However, the present data suggest that these nodules can be evaluated in the same way as nodules in patients without a history of ionizing radiation. . . . If there is a history of ionizing radiation and one cannot feel any nodule . . . [I] would not get a scan. However, if a scan does show anything that is cold, this might lead to an operation. We have never seen a situation where nonpalpable lesions in the thyroid have caused any significant clinical disease.

—CALDWELL B. ESSELSTYN, JR., MD, *Cleveland*

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